REMARKS

Entry of the foregoing, and further and favorable reconsideration, in light of the foregoing amendments and the following remarks, are respectfully requested.

By the present Amendment, Independent Claims 50, 80 and 81 have been amended to remove from part (a) of each claim the list of specific targeted system inhibitors. Rather, a specific "wherein" clause has been added to the end of each of these claims to specifically recite that "binding partners in said extracorporeal system are selected from the group consisting of binding partners to: soluble receptors for tumor necrosis factor α and β, interleukin-1 receptor antagonist, soluble receptors for interleukin- 1, and soluble receptors for interleukin-6". Applicant believes that this amendment to the claims makes it absolutely clear that, regardless of any additional elements which could be included in the system as a result of the word "comprising" at line 2 of the claim (as alleged by the Examiner at p. 15 of the Office Action), any binding partner which is a part of the extracorporeal system is limited to those which bind the recited targeted immune system inhibitors. No new matter has been added.

Prior to addressing the specific rejections, Applicants would like to clarify the status of the pending claims. In the prior Office Action dated October 6, 2004, the Examiner examined all of Claims 50-74, 80[1], 81 and 83-86. However, in the present Office Action where the prior art rejections were maintained, the Examiner only referred to Claims 50, 51, 60-65, 69-74, 80 and 81. There is no indication on the record as to why Claims 52-59, 66-68 and 83-86 would have been withdrawn by the Examiner. However, it is believed that Applicant mistakenly referenced as "withdrawn" certain of the claims in question in its "claim identifiers" in the previous

[1] Claim 80 was indicated as withdrawn on the face of the previous Office Action, but was actually substantively examined in the text of the Office Action.

Response. This has been corrected in the present Amendment. As such, it is believed that Claims 50-74, 80, 81 and 83-86 are currently under consideration.

The Examiner rejected the claims under 35 U.S.C. §103(a) as being purportedly unpatentable as follows:

(1) Claims 50, 51, 60-65, 69-74, 80 and 81 over Skurkovich, 5,626,843 ("Skurkovich '843"), in view of Greenblatt;

(2) Claims 50, 51, 60, 61, 66-74, 80 and 81 over Skurkovich '843, in view of Yelavarthi;

(3) Claims 52, 54, 58, and 83-86 over Skurkovich '843, in view of Greenblatt, and further in view of Skurkovich 4,362,155 ("Skurkovich '155"); and

(4) Claims 50, 53, 55-57 and 59 over Skurkovich '843, in view of Greenblatt, and further in view of Skurkovich '155, and further in view of Prusiner et al, 6,221,614.

These rejections, which are substantially the same as in the previous Office Action, are respectfully traversed.

The presently claimed invention relates to an extracorporeal system for reducing the amount of a targeted immune system inhibitor in whole blood, wherein binding partners selected from the group consisting of binding partners to:

-soluble receptors for tumor necrosis factor α and β,

-interleukin-1 receptor antagonist,

-soluble receptors for interleukin- 1, and

-soluble receptors for interleukin-6.

The Examiner relies in each of her rejections, on Skurkovich '843, as allegedly teaching the removal of receptors for tumor necrosis factor (TNF).

However, Skurkovich '843 only discloses that receptors for tumor necrosis factor can be removed in combination with removal of interferon (IFN) or receptors thereto:

"An objective of the present invention is to restore immunity...by removing IFNs together with TNF, and in some cases the receptors therefor..." (Col. 2, ll. 60-63);

"a combined sorbent comprising a first component of antibodies to IFNs, a second component ...and a third component to remove TNF can be used." (Col. 3, ll. 3-7); and

"the invention uses one sorbent for removing IFNs and other substances, often together with their receptors..." (Col. 3, ll. 18-21).

Indeed, the Examples of Skurkovich '843 all relate to preparation of interferon antibodies and columns, and all of the claims of Skurkovich '843 recite that removal of interferon or an interferon receptor is an essential element: (1) a first antibody to interferon, and a second antibody to tumor necrosis factors, and receptors therefor (see Claims 1-9) or (2) one anti-interferon antibody or an antibody to alpha interferon receptor and one anti-gamma interferon antibody or an antibody to gamma interferon receptor (see Claims 10-16). As such, there would have been no motivation for a person of ordinary skill in the art to attempt to stimulate an immune response in the absence of removal of interferon.

The Examiner cites in the present Office Action a disclosure of three lines in the Skurkovich '843 patent in support of her rejection, namely Col. 3, ll. 37-39, which the Examiner alleges "teaches removal of the receptors by itself". However, it is clear from a review of the Skurkovich '843 file history that the Skurkovich '843 patent does not enable "removal of the receptors by itself".

Specifically, the Skurkovich claims were initially directed to methods which involved the removal of "at least one component...selected from the group consisting of alpha interferons, beta interferons, gamma interferons, tumor necrosis factor, HLA class II antigens...". (See, Amendment dated May 12, 1994 from the Skurkovich '843 file history; Exhibit A.) The claims were later amended to recite methods of removing "a plurality of components...selected from the group consisting of alpha interferons, beta interferons, gamma interferons, tumor necrosis factor, HLA class II antigens..." (See, Amendment dated May 8, 1995 from the Skurkovich '843 file history; Exhibit B.) The Examiner rejected these claims under 35 U.S.C. 112, first paragraph as not being enabled, because "it is unpredictable whether the removal of a single mediator or multiple mediators will result in a significant effect." (See, Office Action dated August 23, 2005 at p. 5 from the Skurkovich '843 file history; Exhibit C.) The Examiner maintained the rejection in the Office Action dated June 12, 1996 (Exhibit D), noting the following:

> Even if removal of alpha interferon is shown to be of benefit in treating certain diseases, a showing relating to alpha interferon could not serve as a basis for predicting that removal of, for example, gamma interferon and beta interferon would result in a similar effect, since these are different factors with different activities and potential roles in disease processes.

(Exhibit D at p. 3).

In response, Skurkovich amended its claims to the form in which they were found allowable and were issued, which require the removal of interferon or its receptor. (Amendment dated November 8, 1996; Exhibit E). Moreover, Skurkovich argued that the data it submitted were in support of "the effect of the **combined** antibodies on the antigens" (Exhibit E at p. 7, emphasis added). Moreover, Skurkovich further argued that it was the "**combination** of anti-IFNα and anti-IFNγ or

to either one in combination with an anti-TNF" which lent patentability to their claims. (Exhibit E at p. 10, emphasis added.) As such, the Examiner considered the Skurkovich claims supported and allowable **only** to the extent they required removal of IFN or its receptor. In light of the clear determination by the Examiner that the Skurkovich '843 patent does not support claims wherein interferon or its receptor are not also removed, the Skurkovich '843 patent is not an enabling reference against the present claims, wherein removal of interferon is **excluded**. As such, all of the Examiner's rejections under 35 U.S.C. 103(a) fail and must be withdrawn.

The invention as presently claimed excludes the additional removal of interferon, because the claims recite that the "at least one binding partner" is "**selected from the group consisting of binding partners to:** soluble receptors for tumor necrosis factor α and β, interleukin-1 receptor antagonist, soluble receptors for interleukin- 1, and soluble receptors for interleukin-6". Skurkovich '843 does not disclose or suggest that immunity could be restored in the absence of concurrent removal of interferon or receptors thereto.

The additional references cited by the Examiner do not cure the deficiencies of Skurkovich '843. Greenblatt and Yelavarthi are relied upon by the Examiner only to support her allegation that antibodies to TNF-α exist (see, Official Action at p. 5, third paragraph, and p. 9, second full paragraph, respectively). Like Skurkovich '843, Skurkovich '155 discloses "an absorption system to absorb interferon..." and does not even mention tumor necrosis factor, interleukin, or receptors thereto. Prusiner discloses the removal of prions from the blood, and does not even mention tumor necrosis factor, interleukin, or receptors thereto.

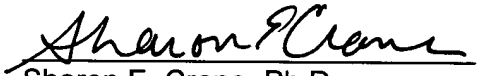
As such, none of the cited references, alone or in combination, discloses or suggests a system for the removal of soluble receptors for tumor necrosis factor α and β, interleukin-1 receptor antagonist, soluble receptors for interleukin- 1, and soluble receptors for interleukin-6, in the absence of removal of interferon or receptors thereto. Withdrawal of these rejections is therefore respectfully requested.

In view of the foregoing, it is believed that the claims are in condition for allowance, and early and favorable action in the form of a notice of allowance is respectfully requested.

In the event that there are any questions relating to this Amendment or to the application in general, it would be appreciated if the Examiner would contact the undersigned attorney by telephone at (202) 778-6150 so that prosecution of the application may be expedited.

Respectfully submitted,
BINGHAM MCCUTCHEN, LLP

Date: July 19, 2005

By: 
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CeP 1806

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of:

SKURKOVICH et al.

Appl. No. 08/025,408 Group Art Unit: 1806

Filed: 26 February 1993 Examiner: unknown

Title: TREATMENT OF AUTOIMMUNE DISEASES, INCLUDING AIDS BY THE REMOVAL OF DIFFERENT TYPES OF INTERFERONS, OTHER PATHOLOGICAL FACTORS AND ANTIBODIES TO TARGET CELLS

12 May 1994

Preliminary Amendment

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In the above referenced divisional application, please preliminarily amend the attached filing as follows:

In the Specification

Page 7, line 2, after "hybridoma" insert --(any monoclonal antibody, however it is produced, as long as it comprises human protein)--.

In the Claims

Please amend claim 1 as follows:

1. (Amended) A method of treatment for autoimmune diseases and AIDS comprising the steps of:

drawing fluid from a patient;

passing said fluid through immunosorbent means for removing at least one component of said fluid selected from the group consisting of alpha interferons, beta interferons, gamma interferons, tumor necrosis factor, HLA class II antigens, immunoglobulin E, antibody to streptococcus group A, antibody to target cells, antibody to CD4 cells, antibody to DNA, antibody to cardiac antigens, [antibody to streptococcus group A,] antibody to joint antigen, and antibody to cerebral antigens;

returning said fluid to said patient.

Please appended new claims 42-53 as follows:

42. A method of treatment for autoimmune diseases and AIDS comprising the step of:

administering at least one of a group consisting of antibodies to alpha interferons, antibodies to beta interferons, antibodies to gamma interferons, and antibodies to tumor necrosis factor.

43. The method according to claim 42, wherein said administration is a parenteral injection.

44. The method according to claim 43, wherein said parenteral injection occurs subcutaneously.

45. The method according to claim 43, wherein said parenteral injection occurs intramuscularly.

46. The method according to claim 43, wherein said parenteral injection occurs intravenously.

47. The method according to claim 42, wherein each said at least one of the group of antibodies is a polyclonal antibody.

48. The method according to claim 42, wherein each said at least one of the group of antibodies is a monoclonal antibody.

49. The method according to claim 42, wherein said group of antibodies includes at least one monoclonal antibody and at least one polyclonal antibody.

50. The method according to claim 42, further comprising the step of:

producing each said at least one of the group of antibodies in human hybridoma.

51. The method according to claim 42, further comprising the step of:

producing each said at least one of the group of antibodies in mice hybridoma.

52. The method according to claim 42, further comprising the step of:

producing at least one of said group of antibodies in human hybridoma and at least one of said group of antibodies in mice hybridoma.

53. A method of treatment for autoimmune diseases and AIDS comprising the steps of:

drawing fluid from a patient;

passing said fluid through immunosorbent means for removing at least one component of said fluid selected from the group

consisting of alpha interferons, beta interferons, gamma interferons tumor necrosis factor, HLA class II antigens, immunoglobulin E, antibody to streptococcus group A, antibody to target cells, antibody to CD4 cells, antibody to DNA, antibody to cardiac antigens, antibody to joint antigen, and antibody to cerebral antigens;

returning said fluid to said patient; and

supplementally administering to said patient at least one of a group consisting of antibodies to alpha interferons, antibodies to beta interferons, antibodies to gamma interferons, and antibodies to tumor necrosis factor.

Remarks

The amendment to the Specification provides Applicants' definition of "human hybridoma" as comprising human protein, whether it is produced in humans or mice, for instance. Support for this revision may be found in the original specification at page 6, lines 23-24.

The amendments to claim 1 simply incorporate an antigen (antibodies to CD4 cells) which was described in the original specification (page 5, lines 15-22), but inadvertently omitted from claim 1; and reorganize the originally claimed sequence of antigens for the sake of logical clarity.

New claims 42-53 are directed to subject matter disclosed in the Specification as originally filed, but which was inadvertently omitted from claims 1-41 initially filed 26 February 1993.

Specifically, claims 42-52 are directed to the administration of antibodies to IFNs and TNF, such as by parenteral injection. Support for this subject matter may be found at page 6, line 26 to page 7, line 4. Claim 53 is directed to the combined use of an immunosorbent column with a supplemental administration of antibodies. Support for this subject matter may be found at page 7, lines 4-6.

Should the Examiners believe additional discussion would advance the prosecution of the present application, they are invited to contact the undersigned at the local telephone number listed below.

Respectfully submitted,
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IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re Application of: SKURKOVICH et al.

Appl. No. 08/025,408 Group Art Unit: 1806

Filed: 26 February 1993 Examiner: Hutzell, P.

Title: TREATMENT OF AUTOIMMUNE DISEASES, INCLUDING AIDS BY THE REMOVAL OF DIFFERENT TYPES OF INTERFERONS, OTHER PATHOLOGICAL FACTORS AND ANTIBODIES TO TARGET CELLS

8 May 1995

Amendment

Hon. Commissioner of Patents
and Trademarks
Washington, D.C. 20231

Sir:

In response to the Office Action mailed 6 December 1994, please enter the following amendments in the above referenced application and reconsider the application in amended form. A petition to extend the period for response up to and including the date of this response is being filed concurrently herewith.

In the Specification

Page 5, line 11, after delete "(i.e. α TNF)".

In the Claims

Please amend claims 1, 42 and 53 as follows:

1. (Third Amendment) A method of treatment for autoimmune diseases and AIDS comprising the steps of:

drawing fluid from a patient;

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passing said fluid through immunosorbent means for removing [at least one component] a plurality of components of said fluid selected from the group consisting of alpha interferons, beta interferons, gamma interferons, tumor necrosis factor, HLA class II antigens, immunoglobulin E, antibody to target cells, antibody to CD4 cells, and antibody to DNA;

returning said fluid to said patient.

42. (Amended) A method of treatment for autoimmune diseases and AIDS comprising the step of:

administering [at least one] a plurality of a group consisting of antibodies to alpha interferons, antibodies to beta interferons, antibodies to gamma interferons, and antibodies to tumor necrosis factor.

53. (Amended) A method of treatment for autoimmune diseases and AIDS comprising the steps of:

drawing fluid from a patient;

passing said fluid through immunosorbent means for removing [at least one component] a plurality of components of said fluid selected from the group consisting of alpha interferons, beta interferons, gamma interferons, tumor necrosis factor, HLA class II antigens, immunoglobulin E, antibody to target cells, antibody to CD4 cells, antibody to DNA;

returning said fluid to said patient; and

supplementally administering to said patient at least one of a group consisting of antibodies to alpha interferons, antibodies to beta interferons, antibodies to gamma interferons, and antibodies to tumor necrosis factor.

Please insert new claims 54-56 as follows:

54. A method of treatment for autoimmune diseases and AIDS comprising the steps of:

drawing fluid from a patient;

passing said fluid through immunosorbent means for removing at least one component of said fluid selected from the group consisting of beta interferons, gamma interferons, tumor necrosis factor, HLA class II antigens, immunoglobulin E, antibody to target cells, antibody to CD4 cells, antibody to DNA;

returning said fluid to said patient.

55. A method of treatment for autoimmune diseases and AIDS comprising the step of:

administering at least one of a group consisting of antibodies to beta interferons, antibodies to gamma interferons, and antibodies to tumor necrosis factor.

56. A method of treatment for autoimmune diseases and AIDS comprising the steps of:

drawing fluid from a patient;

passing said fluid through immunosorbent means for removing at least one component of said fluid selected from the group

consisting of beta interferons, gamma interferons, tumor necrosis factor, HLA class II antigens, immunoglobulin E, antibody to target cells, antibody to CD4 cells, antibody to DNA;

returning said fluid to said patient; and

supplementally administering to said patient at least one of a group consisting of antibodies to alpha interferons, antibodies to beta interferons, antibodies to gamma interferons, and antibodies to tumor necrosis factor.

Remarks

The Examiner is thanked for the Office Action mailed 6 December 1994, as well as the many courtesies extended to the applicants and the undersigned during the course of a personal interview on 20 March 1995. This amendment and request for reconsideration is intended to be fully responsive thereto.

At the time of the Office Action, claims 1-13, 24-37 and 42-53 were pending, with claims 1, 11, 12 and 24-26 under consideration. Claims 2-10, 13, 27-37 and 42-53 were withdrawn from consideration. In view of the following remarks, consideration of the withdrawn claims is respectfully requested on the basis they require the same essential feature as the claims currently under consideration.

The literature discussed below addresses the role of cytokines in the progression of AIDS and other autoimmune diseases. Cytokines play a very important pathological role, and their removal is very beneficial.

Alpha interferon was the first cytokine recognized as playing a role in the pathogenesis of autoimmune disease[1]. It was found to be hyperproduced in an unusual form, and its presence in the blood of patients with an autoimmune disease is a marker for the autoimmune disease[1]. Later, it became evident that αIFN induced αTNF[2] and, together with immune complexes and certain other factors, induced γIFN[3]. Alpha and gamma IFN have been found in the blood of patients with autoimmune diseases[1], and some cytokines have been found locally, such as αIFN in psoriatic lesions[4], in the pancreas in patients with insulin dependant diabetes mellitus[5], in the brain in lupus psychosis[6], and in the cerebrospinal fluid of

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[1] Skurkovich S., Eremikina E.; "The Probable role of Interferon in Allergy"; Ann Allergy 1975; 35:356.

[2] Lau A.S., Livesey J.F.; "Endotoxin induction of Tumor Necrosis Factor in Enhanced by Acid-Labile Interferon-Alpha in Acquired Immunodeficiency Syndrome"; J Clin Invest 1989; 84:738.

[3] Stewart W.; "The Interferon System"; Springer: New York, 1979.

[4] Livden J.K., Nilsen R., Bjerke J.R., Matre R.; "In situ Localization of Interferons on Psoriatic Lesions"; Arch Dermatol Res; 1989; 281:392.

[5] Foulis A.K., Farquharson M.A., Meager A.; "Immunoreactive Alpha-Interferon in Insulin-Secreting Beta Cells on Type 1 Diabetes Mellitus"; Lancet; 1987; 2:1423.

[6] Shiozawa S., Kuroki Y., Kim. Hirohata S., Ogino T.; "Interferon-Alpha in Lupus Psychosis"; Arthr Rheum; 1992; 35:417.

some psychiatric cases[7]. Gamma IFN and TNF were also found in joints[8]. Healthy people do not have these cytokines in the blood or cerebrospinal fluid.

Various autoimmune diseases may also come from a genetic predisposition or under the influence of certain viruses. According to which organ is affected, there are different clinical manifestations. Hyperproduced αIFN and γIFN can provoke autoimmune disease in patients with a genetic predisposition or exacerbate an underlying condition. Alpha or gamma IFN given to cancer patients as a treatment, in cases where patients are already genetically predisposed, can induce different autoimmune diseases. Examples include injections of natural or recombinant αIFN (and sometimes γIFN) to cancer patients to trigger or exacerbate autoimmune parotitis, epididymitis and thyroiditis, SLE, rheumatoid arthritis, vasculitis, Graves' disease, as well as other autoimmune conditions[9,10,11,12]. Alpha IFN injections to patients with

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[7] Libikova H., Breier S., Coscisova M., et al.; "Assay of Interferon and Viral Antibodies in the Cerebrospinal Fluid in Clinical Neurology and Psychiatry"; Acta Biol Med Ger; 1979; 38:879-893.

[8] Holt I., Cooper R.G., Denton J., et al,; "Cytokine Inter-relationships and Their Association with Disease Activity in Arthritis"; B J of Rheumatology; 1992; 31:725-33.

[9] Conlon K.C., Urba W.J., Smith II J.W., et al.; "Exacerbation of Symptoms of Autoimmune Disease in Patients Receiving Alpha-Interferon Therapy"; Cancer; 1990; 65:2237.

[10] Bevan P.C.; "Interferon-Induced Parotitis and Epidymitis"; Lancet; 1985; 2:561.

different types of viral hepatitis induced autoimmune conditions in the liver[13]. A patient with multiple sclerosis given recombinant αIFN subcutaneously and another given recombinant γIFN intrathecally had exacerbation rates significantly higher than expected[14,15]. Administration of αIFN to patients with psoriasis (a disease with an autoimmune component) can cause exacerbation of clinical course[16]. If αIFN is given to mice models of insulin dependant diabetes mellitus, they will develop diabetes more rapidly[17]. In experimental work, antibodies to αIFN or γIFN given to animals with an autoimmune condition, will delay or inhibit the

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[11] Schilling P.J., Kurzrock R., Kantarjian H., et al.; "Development of SLE After Interferon Therapy for Chronic Myelogenous Leukemia"; Cancer; 1991; 68:1536.

[12] Ronnblom L.E., Alm G.V., et al.; "Autoimmunity After Alpha-Interferon Therapy for Malignant Carcinoid Tumors"; Ann of Internal Med; 1991; 115:178.

[13] Fattovich G., Betterle C., Brollo L., et al.; "Autoantibodies During Alpha Interferon Therapy for Chronic Hepatitis"; B J Med Virol; 1991; 34:132.

[14] Larrey D., Marcellin P., Freneaux E., et al.; "Exacerbation of Multiple Sclerosis After the Administration of Recombinant Human Interferon-Alpha"; JAMA; 1989; 261:2065.

[15] Paniteh H.S., Hirsch R.L., Haley A.S., Johnson K.P.; "Exacerbations of Multiple Sclerosis in Patients Treated with Gamma Interferon"; Lancet; 1987; 1:893.

[16] Kusec R., Ostojic S., et al.; "Exacerbation of Psoriasis After Treatment with Alpha-Interferon"; Dermatologica; 1990; 181:2.

[17] Stewart T.A., Hultgren B., Huang X., et al.; "Induction of Type I Diabetes by Interferon-Alpha in Transgenic Mice"; Science; 1993; 260:1942.

disease[16,18]. Antibody to TNF given to humans with RA will improve disease[19]. Thus, because αIFN induces TNF and participates in the induction of γIFN, we talk about a synergistic effect in the pathogenesis of autoimmune disease.

Synovial and cerebrospinal fluids are isolated from the blood stream. Substances in the blood cannot reach these areas, but we must remember that many cytokines are produced and circulate in these areas and, as in blood, have pathological effects. In many psychiatric and neurological autoimmune diseases, cytokines have been found in the CSF and blood[7]. In rheumatoid arthritis, cytokines are found in joints[8]. These cytokines must be removed with extracorporeal methods namely, by passage of the synovial fluid and CSF over a column containing appropriate antibodies.

Acquired Immune Deficiency Syndrome (AIDS) is as an example of an autoimmune disease[20]. Just as in classic autoimmune diseases, the main marker of AIDS progression is the production of αIFN, that

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[18] Tang H., Mignon-Godefroy K., Meroni P.L., et al.; "The Effects of a monoclonal Antibody to Interferon-Gamma on Experimental Autoimmune Thyroiditis (EAT): Prevention of Disease and Decrease of EAT Specific T-Cells"; Eur J Immunol; 1993; 23:275-278.

[19] Elliott M.J., Meini R.N., Feldmann M., et al.; "Randomized Double-Blind Comparison of Chimeric Monoclonal Antibody to Tumor Necrosis Factor-Alpha (cA2) Versus Placebo in Rheumatoid Arthritis"; Lancet; 1994; 344:1105.

[20] Kion K.A. and Hoffman G.W.; "Anti-HIV and Anti-Anti-MHC Antibodies in Alloimmune and Autoimmune Mice"; Science; 1991; 253:1138.

is, an unusual pH labile form of αIFN. Specifically, the progression of AIDS is directly correlated with increasing levels of pH labile αIFN in the blood of AIDS patients[21]. HIV increases the pH labile αIFN production, which induces TNF and γIFN[22]. TNF-alpha induces or increases HIV replication and induces HIV expression[23,24]. When αIFN is given to AIDS patients, a drop in CD4+ cells has been observed[25]. Thus there is an interrelationship between different cytokines induced by HIV which also help the virus replicate. This brings a condition of immunological chaos. Antibody to αIFN or to αIFN receptors, could have a beneficial

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[21] Biglino A., Surbone A., Lipani N., et al.; "Spontaneous Release of Interferon as a Predictor of Clinical Evolution in HIV-Positive Subjects"; Infection; 1991; 19:11.

[22] Vyakarnam A., McKeating J., et al.; "Tumor Necrosis Factors (Alpha, Beta) induced by HIV-1 in Peripheral Blood Mononuclear Cells Potentiate Virus Replication"; AIDS; 1990; 4:21.

[23] Poli G., Kinter A., Justement J., et al.; "Tumor Necrosis Factor Alpha Functions in an Autocrine Manner in the Induction of Human Immunodeficiency Virus Expression"; Proc Natl Acad Sci USA; 1990; 87:782.

[24] Mateuyama T., Kobayashi N. and Yamamoto N.; "Cytokines and HIV Infection: is Aids a Tumor Necrosis Factor Disease?"; AIDS; 1991; 5:1405.
Mauritz N.J., Holmadahl R., Jonsson R., et al.; "Treatment with Gamma-Interferon Triggers the Onset of Collagen Arthritis in Mice"; Arthr and Rheum; 1988; 31:1297.

[25] Vento S., DiPerri G., et al.; "Rapid Decline of CD4+ Cells after IFN-alpha Treatment in HIV-1 Infection"; Lancet; 10 April 1993; 341.

effect[26,27]. Also, when antibody to γIFN is given to a murine model of AIDS, the condition improves[28]. Antibodies to all three of these cytokines (αIFN, γIFN and TNF) could prove very beneficial. NIH is now advocating the blocking of cytokines as a treatment for AIDS[29]. The main laboratory manifestation of AIDS is CD4+ cell loss. Because AIDS is also an autoimmune disease, it is possible that antibody to CD4 plays a part in this loss since anti-CD4 antibodies have been found in the blood of AIDS patients. To remove this CD4 antibody from the plasma, we must use extracorporeal methods in which CD4 cells are contained in the extracorporeal cartridge. Thus, for an effective treatment for AIDS and autoimmune disease, a combined method, injection and extracorporeal removal, is preferred.

Therefore, an object of the present invention is the partial or complete reconstitution of an immune system affected by AIDS or

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[26] Tovey M.G., Lebon P., Meyer F., et al.; "Antibody to the Human IFN-Alpha Receptor Reduces the Loss of CD4+ T-Cells in Macaques Infected with the Simiian Immunodeficiency Virus (SIV)"; J Interferon Res; 1993; 13, abstract W17-2.

[27] Swindelle S., Skurkovich S., et al.; "IFN-Pheresis: a Novel Therapeutic for Altering Immune Function in HIV disease"; First National Conference on Human Retroviruses and Related Infections - program and abstracts; 1993; 74.

[28] Uehara S., Hitoshi Y., et al.; "Role of IFN-Gamma in the Development of the Murine Acquired Immunodeficiency Syndrome, MAIDS"; J Interferon Res; 1993; 13:abstract PW6-9.

[29] Fauci A.S.; "Multifactorial Nature of Human Immunodeficiency Virus Disease: Implications for Therapy"; Science; 1993; 262:1011.

another autoimmune disease. The essence of the present invention is the **reduction of cytokines** in blood or various other body fluids (claims 24-26). As such, the present invention differs from previous approaches to control AIDS and other autoimmune diseases which use immunotherapy, i.e. the administration of antibodies to directly treat cells already afflicted with an autoimmune disease. That is to say, the present invention is directed to treating a key pathogenetic link in the chain of reactions involved in the development of the disease rather than the disease itself.

The present invention is directed to anti-cytokine treatment wherein cytokines are removed and/or neutralized for the purposes of reducing severity of the disease and prolonging longevity. According to twice amended claim 1, and all the claims which depend therefrom, a plurality of cytokines selected from the group consisting of alpha interferons, beta interferons (βIFN), gamma interferons, tumor necrosis factor, HLA class II antigens, immunoglobulin E (IgE), antibody to target cells, antibody to CD4 cells, and antibody to DNA are reduced.

The essential anti-cytokine treatment according to the present invention may be accomplished by approaches including extracorporeal filtering of cytokines (claims 1-13 and 24-37), administering antibodies to the cytokines (claims 42-52), or the combination of both (claim 53). Inasmuch as the various approaches to the anti-cytokine treatment are secondary to the specified treatment itself, it is respectfully suggested that the claims

previously withdrawn from consideration may rightfully be re-introduced.

The Preliminary Amendment filed 19 November 1994 was objected to under 35 U.S.C. § 132 for the reason given in paragraph 17 of the Office Action. This objection is respectfully traversed in view of the cancellation of the objectionable insertion.

Claims 1, 11, 12 and 24-26 were rejected under 35 U.S.C. § 101 for the reasons given in paragraph 18 of the Office Action. As addressed during the interview, and noted on the Examiner Interview Summary Record, this rejection will be withdrawn in view of recent judicial action.

Claims 1, 11, 12 and 24-26 were rejected under 35 U.S.C. § 112, first paragraph, for the reasons given in paragraph 19 of the Office Action. This rejection is respectfully traversed in view of the following remarks.

Examples of specific anti-cytokine treatments are associated with particular diseases (page 5, line 13 to page 6, line 17). Explanations of various approaches for effecting anti-cytokine treatments are discussed on page 6, line 21 to page 8, line 12. Examples of how to produce and use anti-cytokine material are provided on page 8, line 15 through page 9, line 17. Inasmuch as the present invention is directed to the reduction of cytokines present at any time during the progression of an autoimmune disease, there are no parameters such as specific time points for the treatment or duration of treatment.

Therefore, no experimentation is required to practice the present invention, rather it is necessary only to implement reduction of cytokines according to the present invention.

Claim 1 was rejected under 35 U.S.C. § 102(b) as anticipated by Skurkovich et al. (US #4,824,432). Claims 1 and 12 were rejected under 35 U.S.C. § 102(b) as anticipated by Skurkovich (US #4,362,155). Claims 24-26 were rejected under 35 U.S.C. § 103 as being unpatentable over either the '432 or the '155. Claim 1 was rejected under 35 U.S.C. § 103 as being unpatentable over Skurkovich (US #4,605,394). These rejections are respectfully traversed in view of the above amendments and the following arguments.

Each of these rejections applies the previous teachings of the present Applicants. Whereas the present invention is directed to the reduction of a combination of cytokines, Applicants' prior teachings are directed to solely treating αIFN. It is emphasized that the present invention describes an approach which is not merely additive in view of Applicants' prior art, but has a synergistic effect on the pathological progression of autoimmune diseases.

With regard to claims 24-26, it is generally difficult in clinical medicine to deliver therapeutic substances to the actual site where a pathological process is progressing. For example, antibiotics do not penetrate well into cerebrospinal fluid or joints. It is respectfully submitted that the removal of cytokines

from synovial fluid, intraperitoneal fluid and cerebrospinal fluid is not an obvious modification of removing αIFN from blood as taught in Applicants' prior patents.

Claims 1 and 24-26 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-33 of the '432, as well as over claims 1 and 2 of the '394. Claims 1, 12 and 24-26 were rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 10-12 of the '155. These rejections are respectfully traversed in view of the previous remarks concerning the prior art and further in view of the following remarks.

Inasmuch as the present invention is directed to a distinct invention for the reasons discussed above, it is respectfully submitted that no double patenting exists. Similarly, it is respectfully submitted that Applicants' prior teachings, in combination with any prior art of record or the common knowledge of one of ordinary skill, are not suggestive of the present invention.

In order to resolve the questions raised with regard to 35 U.S.C. § 102(f) or (g), each of the aforementioned prior art teachings and the present application were commonly owned at the time of this application. In particular, the '432, '155, and '394 are commonly owned either by the Applicants, or by entities wholly owned by the Applicants.

Finally, with regard to the rejection under 35 U.S.C. § 102(f) in view of the publication in Medical Hypotheses, Applicants have appended hereto a statement to the effect that the contribution of Dr. Bellanti was limited to assistance in the preparation of the presentation for publication, and that Dr. Bellanti has neither participated in, nor contributed to the development of the subject matter which forms the basis of the present invention.

New claims 54-56 have been added to encompass treatment by the different approaches, excluding αIFN. It is respectfully submitted that these claims also embody a novel and unobvious feature of the present invention, i.e. the reduction of cytokines.

It is respectfully suggested that the present application is now in condition for allowance and notice to that effect is earnestly solicited. Should the Examiners believe additional discussion would advance the prosecution of the present application, they are invited to contact the undersigned at the local telephone number listed below.

Respectfully submitted,
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UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/025,408	02/26/93	SKURKOVICH	~~ARC01/00008~~

EXAMINER	
HUTZELL, P	
ART UNIT	**PAPER NUMBER**
1806	16

18M2/0823

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DATE MAILED: 08/23/95

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 5/8/95 ☐ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☒ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-13, 24-37 and 42-56 are pending in the application.
   Of the above, claims _____ are withdrawn from consideration.
2. ☒ Claims 14-23 and 38-41 have been cancelled.
3. ☐ Claims _____ are allowed.
4. ☒ Claims 1-13, 24-37 and 42-56 are rejected.
5. ☐ Claims _____ are objected to.
6. ☐ Claims _____ are subject to restriction or election requirement.
7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.
8. ☐ Formal drawings are required in response to this Office action.
9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).
10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).
11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).
12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____; filed on _____.
13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.
14. ☐ Other

15. The status of the claims is as follows: Claims 1-13, 24-37 and 42-56 are presently under consideration and have been amended as requested by applicant in the communication filed on 5-8-95. Claims 14-23 and 38-41 have been canceled. The restriction requirement set forth in Paper No. 8 has been withdrawn upon further search and consideration.

15. The objection to the specification under 35 U.S.C. § 132 is withdrawn.

16. The rejection of claims 1, 11, 12 and 24-26 under 35 USC § 101 is withdrawn.

17. The objection to the specification under 35 USC § 112, first paragraph is maintained for reasons of record in paragraph 19 of the previous office action.

The record contains insufficient evidence to allow one of skill in the art to practice the broadly claimed methods for treatment of autoimmune diseases and AIDS with a reasonable expectation of success.

The claimed invention relates to the highly complex and unpredictable area pertaining to the development of effective immunotherapy methods for the treatment of AIDS and autoimmune disease. The state of the art to which the invention pertains is such that the underlying mechanisms of AIDS and autoimmune diseases are incompletely understood which has been an impediment to the development of and effective immunotherapies. The obstacles to the development of therapeutic approaches with regard to the

treatment of HIV-1 infection in humans are well documented in the scientific literature as are the obstacles to the development of effective therapeutic approaches for the treatment of autoimmune diseases. The term "autoimmune disease" is generic to a large number of diseases of different and unrelated pathologies and etiologies. The underlying mechanisms of most autoimmune diseases are incompletely understood and the diseases in general, have been refractory to effective immunotherapy. Due to the extreme complexity of autoimmune diseases and the involvement of multiple mediators in the disease processes, it is unpredictable whether the removal of a single mediator or multiple mediators will result in a significant therapeutic effect. Skurkovich et al. (Medical Hypotheses 41) support the examiners assessment of the state of the art as to the lack of an art-established role of interferons and other mediators in AIDS and autoimmune diseases in teaching that the efficacy of methods involving the removal of interferons, autoantibodies, etc. from organisms for treatment of autoimmune disease and AIDS is hypothetical and has not been definitively established. The reference makes numerous statements as to the "possible role" of the IFN system in the development of AIDS and autoimmune disease, and proposes that the removal of IFNs and other mediators from the blood "may" help in the management of AIDS and autoimmune diseases (See for example, page 179, col. 1; page 181, col 2, last sentence). Additionally, the inventions of claims 42-52 involve only the administration of antibodies. Harris et al.,

cited of interest, establish that the state of the art relating to the treatment of human diseases by the administration of antibodies is such that those skilled in the art accept that rodent antibodies are generally ineffective for the treatment of human diseases for a number of reasons which are discussed on page 42. While the specification contemplates the use of human monoclonal antibodies, no teaching of how to obtain therapeutically useful human monoclonal antibodies. The ability to obtain therapeutically useful human monoclonal antibodies is well recognized in the art to be unpredictable and difficult (See Co et al., cited of interest). The specification provides no direction or guidance with regard to properties which characterize antibodies that are suitable for use in the claimed methods to assist one of skill in the art in practicing the methods of claims 27-35, 42-53, 55 and 56. Those of skill in the art would not readily accept the asserted efficacy of the claimed methods in the absence of convincing experimental evidence and could not practice the claimed methods with a reasonable expectation of success in the absence of a detailed description and working examples.

Applicant has cited numerous references in support of the argument that the specification enables the practice of the claimed methods without undue experimentation. However, copies of the references have not been provided for the examiner's evaluation. In the absence of objective evidence in support of applicant's arguments, the arguments are not persuasive.

Claims 1-13, 24-37 and 42-56 are rejected under 35 U.S.C. § 112, first paragraph, for the reasons set forth in the previous office action.

18. Claims 1 and 54 are rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,824,423.

Claims 1 and 12 remain rejected and new claim 54 is rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Patent No. 4,362,155.

Claims 24-26 remain rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 4,824,423 or U.S. Patent No. 4,362,155.

Claims 1 and 54 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 4,605,394 for reasons of record.

In response to the above rejections, applicant argues that applicant's prior teachings are directed to the reduction only of alpha interferon. This argument has been fully considered but is not found to be persuasive. U.S. Patent No. 4,824,423 contains claims directed to the removal of a plurality of components from blood. The patent teaches extracorporeal treatment of blood using an immunosorbent containing anti-alpha interferons and additionally, immunosorbents to microorganisms or to HTLV-III/LAV, both of which meet the requirements of claims 1 and 12 of removing "target cells". U.S. Patent No. 4,362,155 teaches treatment of blood with a combined sorbent having a first component made of an antibody against IgE or DNA and a second antibody against alpha

interferon. U. S. Patent No. 4,824,432 contemplates clearance of alpha interferons and other interferons as well as antibodies to HTLV-III/LAV virus, microorganisms and other substances.

19. Claims 1, 24-26 and 54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 27-33 of U.S. Patent No. 4,824,432.

Claims 1, 12, 24-26 and 54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-7 and 10-12 of U.S. Patent No. 4,362,155.

Claims 1, 24-26 and 54 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-2 of U.S. Patent No. 4,605,394.

Applicant has traversed these rejections on the basis of essentially the same arguments as set forth in response to the rejections in paragraph 18, above. These arguments are not found to be persuasive for reasons set forth in paragraph 18.

20. Applicant's response to paragraph 25 of the previous office action is noted. A showing of evidence which establishes that the present invention and those claimed in claims 27-33 of U.S. Patent No. 4,824,432, claims 1-7 and 10-12 of U.S. Patent No. 4,362,155, and claims 1-2, of U.S. Patent No. 4,605,394 were commonly owned at the time the later invention was made, is required.

21. The rejection of claims 1, 11, 12 and 24-26 under 35 U.S.C. § 102(f) found in paragraph 26 of the previous office action is

withdrawn.

The following are new rejections:

22. Claims 1-5, 10, 11, 27-30, 36, 37 and 42-56 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 4,824,432.

The '432 patent teaches methods for the treatment of autoimmune diseases and AIDS comprising administering antibodies specific for alpha interferons and other interferons as well as antibodies to HTLV-III/LAV virus and other microorganisms. The '432 patent also teaches methods of treating AIDS and autoimmune diseases by removal of interferon alpha, other interferons, HTLV-III/LAV and other microorganisms and substances by immunosorbent means. In addition to the clearance of interferons by the above approaches, the '432 patent suggests clearance of HTLV-III/LAV virus and microorganisms and other substances which cause opportunistic infections by the immunosorbent approach or by the administration of antibodies to HTLV-III, microorganisms and/or other substances.

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to treat of AIDS and autoimmmune diseases by removal of alpha interferon and other interferons from the blood by the immunosorbent approach described in the '432 patent. It would have been obvious to remove a plurality of interferons alpha, beta and gamma interferons in view of the explicit suggestion in column 2,

lines 30-34 to clear alpha interferons or other types of interferons. The "other types" of interferon referred to are clearly beta IFN and gamma IFN.

Alternatively, it would have been obvious to clear alpha and/or other interferons by administration of antibodies specific for alpha and other interferons in view of the teaching of the '432 patent that as an alternative to the immunosorbent approach, interferons can be cleared by administration of antibodies.

In both the immunosorbent methods and direct injection methods, it would have been obvious to clear target cells such as those expressing HIV-related antigens e.g. gp120, or to clear target cells using anti-microorganism antibodies or to clear "other substances" in view of the teachings in columns 2-3.

The '432 patent teaches that antibodies used in the methods described therein include monoclonal antibodies, polyclonal antibodies and human antibodies. The '432 patent teaches that antibodies administered according to the direct injection method may be administered IV and IM.

It would have been obvious to combine the therapeutic approaches taught in the '432 patent and to employ both the immunosorbent and direct antibody injection approaches for the treatment of autoimmune diseases and AIDS. The idea of combining the two approaches flows logically from their having been individually taught in the prior art to be useful for the same purpose. In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

23. Claims 1-7, 10, 11, 27-30, 36, 37 and 42-56 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 4,824,432 taken with Moller (U.S. Patent No. 5,231,024).

The teachings of the '432 patent have been previously characterized.

Moller teaches anti-TNF antibodies and suggests that the antibodies can be used to treat autoimmune diseases. Moller teaches that antibodies may be administered to mammals and can be used to extract TNF from biological materials by immunoaffinity chromatography.

It would have been prima facie obvious to one of ordinary skill in the art to combine the teachings of the cited references and to use antibodies to interferons and antibodies to TNF to clear interferons and TNF from biological materials either by immunosorbent means or direct injection.

The idea of combining the two approaches flows logically from their having been individually taught in the prior art to be useful for the same purpose. In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

24. Claims 11-13 and 27-30 are rejected under 35 U.S.C. § 103 as being unpatentable over U.S. Patent No. 4,824,432 taken with Moller (U.S. Patent No. 5,231,024) and U.S. Patent 4,362,155.

U.S. Patent No. 4,362,155 teaches treatment of blood with a combined sorbent having a component made of an antibody DNA and a second antibody against alpha interferon. It would have been obvious to combine the teachings of the cited references and to use

antibodies to interferons and TNF and antibodies to DNA to clear these components from biological materials either by immunosorbent means or direct injection. The idea of combining these approaches flows logically from their having been individually taught in the prior art to be useful for the same purpose. In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Paula Hutzell, Ph.D, whose telephone number is (703) 308-4310. The Examiner can normally be reached on Monday-Thursday from 9:00 AM-6:00 PM. The Examiner can also be reached on alternate Fridays.

If attempts to reach the Examiner by telephone are unsuccessful, the Examiner's Supervisor, Margaret Parr, can be reached on (703)-308-2454. The fax phone number for this Group is (703)-305-7401.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

No claim is allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Examiner Paula Hutzell, Ph.D, whose telephone number is (703) 308-4310. The Examiner can normally be reached on Monday-Thursday from 9:00 AM-

6:00 PM. The Examiner can also be reached on alternate Fridays.

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Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

PAULA K. HUTZELL
PRIMARY EXAMINER
GROUP 1800

FORM PTO-892 (REV. 2-92)	U.S. DEPARTMENT OF COMMERCE PATENT AND TRADEMARK OFFICE	SERIAL NO.	GROUP ART UNIT	ATTACHMENT TO PAPER NUMBER
NOTICE OF REFERENCES CITED		08/025408	1806	16
		APPLICANT(S) Skurkovich et al.		

U.S. PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	NAME	CLASS	SUB-CLASS	FILING DATE IF APPROPRIATE
	A	5231024	7/1993	Moller et al.			Sep. 1987
	B						
	C						
	D						
	E						
	F						
	G						
	H						
	I						
	J						
	K						

FOREIGN PATENT DOCUMENTS

*		DOCUMENT NO.	DATE	COUNTRY	NAME	CLASS	SUB-CLASS	PERTINENT SHTS. DWG	PERTINENT PP. SPEC.
	L								
	M								
	N								
	O								
	P								
	Q								

OTHER REFERENCES (Including Author, Title, Date, Pertinent Pages, Etc.)

	R	Harris et al. Fibtech 11: 42-44, 1993 Co et al., Nature 351: 501-2, 1991
	S	
	T	
	U	

EXAMINER	DATE	
	7/14/05	

* A copy of this reference is not being furnished with this office action.
(See Manual of Patent Examining Procedure, section 707.05 (a).)

UNITED STATES DEPARTMENT OF COMMERCE
Patent and Trademark Office
Address: COMMISSIONER OF PATENTS AND TRADEMARKS
Washington, D.C. 20231

SERIAL NUMBER	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.
08/025,408	02/26/93	SKURKOVICH S	ABC01/00008

EXAMINER	
HUTZELL	

ART UNIT	PAPER NUMBER
1806	19

18M1/0612

LONGACRE & WHITE
1919 S. EADS STREET, STE. 401
ARLINGTON, VA 22202

DATE MAILED: 06/12/96

This is a communication from the examiner in charge of your application.
COMMISSIONER OF PATENTS AND TRADEMARKS

☒ This application has been examined ☒ Responsive to communication filed on 1-23-96 ☒ This action is made final.

A shortened statutory period for response to this action is set to expire 3 month(s), 0 days from the date of this letter.
Failure to respond within the period for response will cause the application to become abandoned. 35 U.S.C. 133

Part I THE FOLLOWING ATTACHMENT(S) ARE PART OF THIS ACTION:

1. ☐ Notice of References Cited by Examiner, PTO-892.
2. ☐ Notice of Draftsman's Patent Drawing Review, PTO-948.
3. ☐ Notice of Art Cited by Applicant, PTO-1449.
4. ☐ Notice of Informal Patent Application, PTO-152.
5. ☐ Information on How to Effect Drawing Changes, PTO-1474.
6. ☐ _____.

Part II SUMMARY OF ACTION

1. ☒ Claims 1-13, 24-37 and 42-56 are pending in the application.

   Of the above, claims _____ are withdrawn from consideration.

2. ☒ Claims 14-23 and 38-41 have been cancelled.

3. ☐ Claims _____ are allowed.

4. ☒ Claims 1-13, 24-37 and 42-56 are rejected.

5. ☐ Claims _____ are objected to.

6. ☐ Claims _____ are subject to restriction or election requirement.

7. ☐ This application has been filed with informal drawings under 37 C.F.R. 1.85 which are acceptable for examination purposes.

8. ☐ Formal drawings are required in response to this Office action.

9. ☐ The corrected or substitute drawings have been received on _____. Under 37 C.F.R. 1.84 these drawings are ☐ acceptable; ☐ not acceptable (see explanation or Notice of Draftsman's Patent Drawing Review, PTO-948).

10. ☐ The proposed additional or substitute sheet(s) of drawings, filed on _____. has (have) been ☐ approved by the examiner; ☐ disapproved by the examiner (see explanation).

11. ☐ The proposed drawing correction, filed _____, has been ☐ approved; ☐ disapproved (see explanation).

12. ☐ Acknowledgement is made of the claim for priority under 35 U.S.C. 119. The certified copy has ☐ been received ☐ not been received ☐ been filed in parent application, serial no. _____ ; filed on _____.

13. ☐ Since this application apppears to be in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under Ex parte Quayle, 1935 C.D. 11; 453 O.G. 213.

14. ☐ Other

15. Claims 1-13, 24-37, 42-56 are under consideration.

Claims 14-23 and 38-41 are canceled.

16. The objection to the specification and rejection of claims 1-13, 24-37 and 42-56 under 35 USC 112, first paragraph are maintained.

Applicant's arguments and exhibits have been carefully studied but are not found persuasive.

The Fauci reference teaches that as of 1993, which is in the time frame of the effective filing date of this application, the art considered that the approach of blocking cytokine secretion or action "should be explored" (p1014 col.1). This highlights the experimental nature of this field and the lack of validation of this approach for treating AIDS. Gringeri et al. has not been fully evaluated because a complete copy was not submitted (pages 386-387 missing). It does not appear that the study evaluated efficacy, but rather, was directed at evaluating safety and toxicity. The remaining exhibits discuss primarily roles of alpha and gamma interferons and TNF as pathological mediators in HIV infection and certain specific autoimmune diseases. These references do not provide sufficient basis to predict whether removal of these mediators by plasmapheresis using antibody affinity devices will mediate effective therapy of AIDS and all autoimmune diseases since the mediators are constantly produced

in vivo and a sporadic and transient decrease in their levels may be of no consequence in terms of improving clinical status.

The exhibits are directed to a restricted number of mediators whereas the claims are much broader in scope.Even if removal of alpha interferon is shown to be of benefit in treating certain diseases, a showing relating to alpha interferon could not serve as a basis for predicting that removal of, for example, gamma interferon and beta interferon would result in a similar effect, since these are different factors with different activities and potential roles in disease processes. As evidenced by Hess et al. (Exhibit 5), the complexity of the interaction of the cells of the immune system and different factors released is not fully elucidated. Exhibit 5 indicates that interferon gamma production is not generally significantly altered in HIV-infected patients. Thus, it is unpredictable whether the removal of gamma interferon would result in clinical benefit. Further, the Exhibits do not address the potential therapeutic benefit to be obtained by removal of beta interferons, HLA class II antigens, IgE, antibody to target cells, antibody to CD4 positive cells and antibody to DNA. It is unclear as to the involvement, if any, of beta interferons, HLA class II antigens, IgE, antibody to target cells, antibody to CD4 positive cells and antibody to DNA in the pathology of HIV infection. One cannot predict whether removal of any of these substances will be of any benefit in the

treatment of AIDS. It is unclear how removal of CD4-positive cells would be of benefit in treatment of AIDS.

Further, as discussed in previous office actions, the term "autoimmune disease" is generic to a large number of diseases of different and unrelated pathologies and etiologies. The underlying mechanisms of most autoimmune diseases are incompletely understood, [illegible] Due to the extreme complexity of autoimmune diseases and the involvement of multiple mediators in the disease processes, it is unpredictable whether the removal of a particular substance will be effective for treatment of autoimmune diseases in general. While a particular substance may be involved in the pathology of a specific autoimmune disease and its removal may result in some clinical benefit, the substance to be removed is likely to be dictated by the specific disease in question. For example, it is unlikely that removal of anti-DNA antibodies, IgE, will be effective for treatment of autoimmune diseases in general since there is no evidence that these substances are pathological mediators in autoimmune diseases in general. The specification provides no specific direction or guidance identifying the specific substances whose removal is likely to result in clinical benefit for specific autoimmune diseases. The determination of which mediators are important in the pathology of the complex and large number of diseases which are classified as autoimmune diseases

and of how to effectively treat those diseases would constitute undue experimentation.

It is further unclear whether removal of mediators from an unspecified fluid sample will constitute an effective treatment for any and all autoimmune diseases and AIDS. The particular disease would dictate the fluid to be plasmapheresed.

Administration of murine antibodies to clear mediators is not expected to be effective for reasons discussed in the previous action.

17. Claims 24-26 remain rejected under 35 U.S.C. § 103 as being unpatentable over US Pat Nos. 4,824,423 or 4,362,155.

18. Claims 1 and 54 remain rejected under 35 U.S.C. § 102(b) over U.S. Pat. No. 4,824,423.

19. Claims 1 and 54 remain rejected under 35 U.S.C. § 103 over U.S. Pat. No. 4,605,394.

20. Claims 1, 12 and 54 remain rejected under 35 U.S.C. § 102(b) as being anticipated by U.S. Pat. No. 4,362,155.

21. Claims 1-5, 10, 11, 27-30, 36, 37 and 42-56 remain under 35 USC 103 over U.S. Pat. No.4,824,432.

22. Claims 1-7, 10, 11, 27-30, 36, 37 and 42-56 remain rejected over US Pat. No. 4,824,432 taken with U.S. Pat. No. 5,123,024 for reasons as set forth paragraph 23 of the previous action.

23. Claims 11-13 and 27-30 remain rejected under 35 USC 103 over U.S. Pat. Nos. 4,824,432, 5,231,024 and 4,362,155 for reasons of record in paragraph 24 of the previous office action.

In response to the prior art rejections, Applicant argues that Moeller's patent appeared after Skurkovich submitted this invention for patenting. Applicant further argues that Moller mentions in the specification and not the claims, the use of anti-TNF antibodies as a possible treatment for AD. It is further argued that the present application is for the use of a combination of cytokines which will have a synergistic effect and that Moller does not mention the use of anti-TNF as part of a combined therapy. Applicant additionally argues that Patent No. 4,824,432 does not mention removal of gamma IFN.

The above arguments have been fully considered but are not found to be persuasive.

The effective filing date of U.S. patent 5,231,024 (Moller) is September 1987 while that of the present invention is 2/26/93. Thus, Moller qualifies as prior art under 35 USC § 102(e). The fact that Moller does not claim method of use of anti-TNF antibodies for treatment of autoimmune disease is irrelevant. The entire disclosure of Moller is available as prior art.

It would have been obvious to combine the therapeutic approaches taught in the '432 patent and to employ both the immunosorbent and direct antibody injection approaches for the

treatment of autoimmune diseases and AIDS. The idea of combining the two approaches flows logically from their having been individually taught in the prior art to be useful for the same purpose. In re Kerkhoven, 205 USPQ 1069 (CCPA 1980).

Similarly, it would have been obvious to use antibodies to interferons and antibodies to TNF to clear interferons and TNF from biological materials either by immunosorbent means or direct injection. The idea of combining the two approaches would have flowed logically from their having been individually taught in the prior art to be useful for the same purpose.

Applicant has not separately addressed the rejections over U.S. Pat. No. 4,605,394 and U.S. Pat. No. 4,362,155. The rejections are maintained for reasons of record.

24. The double patenting rejections set forth in paragraphs 19-20 of the previous action are maintained applicant has not yet taken appropriate action to overcome the rejections.

No claim is allowed.

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 C.F.R. § 1.136(a).

A SHORTENED STATUTORY PERIOD FOR RESPONSE TO THIS FINAL ACTION IS SET TO EXPIRE THREE MONTHS FROM THE DATE OF THIS ACTION. IN THE EVENT A FIRST RESPONSE IS FILED WITHIN TWO MONTHS OF THE MAILING DATE OF THIS FINAL ACTION AND THE ADVISORY ACTION IS NOT MAILED UNTIL AFTER THE END OF THE THREE-MONTH SHORTENED STATUTORY PERIOD, THEN THE SHORTENED STATUTORY PERIOD WILL EXPIRE

ON THE DATE THE ADVISORY ACTION IS MAILED, AND ANY EXTENSION FEE PURSUANT TO 37 C.F.R. § 1.136(a) WILL BE CALCULATED FROM THE MAILING DATE OF THE ADVISORY ACTION. IN NO EVENT WILL THE STATUTORY PERIOD FOR RESPONSE EXPIRE LATER THAN SIX MONTHS FROM THE DATE OF THIS FINAL ACTION.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Paula Hutzell whose telephone number is (703) 308-4310. The examiner can normally be reached on Monday-Thursday from 8:30-6:00. The examiner can also be reached on alternate Fridays.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Marian Knode, can be reached on 308-4311.

Any inquiry of a general nature or relating to the status of this application should be directed to the Group receptionist whose telephone number is (703) 308-0196.

Hutzell/sg

June 12, 1996

PAULA K. HUTZELL
PRIMARY EXAMINER
GROUP 1800

Amendment Under 37 C.F.R. § 1.116
Expedited Procedure - Art Unit 1806

IN THE UNITED STATES PATENT AND TRADEMARK OFFICE

In re application of:
Skurkovich & Skurkovich
Appl. No.: 08/025,408
Filed: February 26, 1993
For: Treatment of Autoimmune Diseases, including AIDS by the Removal of Different Types of Antibodies to Target Cells

Art Unit: 1806
Examiner: Scheiner, Toni
Atty. Docket: ABC-0001

Amendment and Response Under 37 C.F.R. § 1.116

Hand Carried

Assistant Commissioner for Patents
Washington, D.C. 20231

Sir:

In the above-captioned Application, Applicants submit the following Amendment and Remarks. The Examiner is requested to kindly enter the following Amendment:

In the Title of the Invention:

Please change the title of the invention from "Treatment of Autoimmune Diseases, including AIDS by the Removal of Different Types of Antibodies to Target Cells" to the following:--Treatment of Autoimmune Diseases, including AIDS, by Removal of Interferons, TNFs and Receptors Therefor--.

In the Specification:

Page 3, line 2, please delete "sinovial" and substitute -- synovial--.

Page 5, line 11, please delete "therefore" and substitute -- therefor--.

In the Claims:

Please cancel claims 1-13, 24-37, and 42-56.

Please add the following new claims:

-- 57. A method of removing antigens from a patient with autoimmune disease or AIDS comprising the steps of:

drawing fluid from said patient;

passing said fluid through immunosorbent comprising a combination of antibodies, consisting essentially of: (a) one or more antibodies to at least one interferon, selected from the group consisting of alpha interferons and gamma interferons, and receptors therefor; and (b) one or more antibodies to tumor necrosis factors, and receptors therefor; and

returning said fluid to said patient.

58. The method according to claim 57, wherein said method removes alpha interferon and tumor necrosis factor from said fluid.

59. The method according to claim 57, wherein said method removes gamma interferon and tumor necrosis factor from said fluid.

60. The method according to claim 57, wherein said method removes both alpha and gamma interferon, and tumor necrosis factor, from said fluid.

61. The method according to claim 57, wherein said fluid is selected from the group consisting essentially of blood, plasma, plasma containing leukocytes, peritoneal fluid, cerebrospinal fluid, and synovial fluid.

62. The method according to claim 57, wherein said antibodies are selected from the group consisting of monoclonal antibodies, polyclonal antibodies, and combinations thereof.

7 ~~63~~. The method according to claim 1 ~~57~~, wherein said method removes: (a) one or more receptors for at least one interferon, selected from the group consisting of alpha interferons and gamma interferons, and (b) tumor necrosis factor, from said fluid.

8 ~~64~~. The method according to claim 1 ~~57~~, wherein said method removes: (a) one or more interferons, selected from the group consisting of alpha interferons and gamma interferons, and (b) at least one receptor for tumor necrosis factor, from said fluid.

9 ~~65~~. The method according to claim 1 ~~57~~, wherein said method removes (a) one or more receptors for at least one interferon, selected from the group consisting of alpha interferons and gamma interferons, and (b) at least one receptor for tumor necrosis factor, from said fluid.

D1 continued

10 ~~66~~. A method of removing antigens from a patient with autoimmune disease or AIDS comprising the steps of:

drawing fluid from a patient;

passing said fluid through immunosorbent comprising in combination a plurality of antibodies, consisting essentially of at least one antibody selected from the group consisting of anti-alpha interferon and antibody to alpha interferon receptor, and at least one antibody selected from the group consisting of anti-gamma interferon and antibody to gamma interferon receptor; and

returning said fluid to said patient.

11 ~~67~~. The method according to claim 10 ~~66~~, wherein said fluid is selected from the group consisting essentially of blood, plasma, plasma containing leukocytes, peritoneal fluid, cerebrospinal fluid, and synovial fluid.

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12 ~~68~~. The method according to claim 10 ~~66~~, wherein said antibodies are selected from the group consisting of monoclonal antibodies, polyclonal antibodies, and combinations thereof.

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13 ~~69~~. The method according to claim 10 ~~66~~, wherein said treatment removes both alpha interferon and gamma interferon from said fluid.

14 ~~70~~. The method according to claim 10 ~~66~~, wherein said treatment removes both alpha interferon receptor and gamma interferon receptor from said fluid.

D1 continued

15 ~~71~~. The method according to claim 10 ~~66~~, wherein said treatment removes a combination of: (a) alpha interferon, and (b) receptor for gamma interferon, from said fluid.

16 ~~72~~. The method according to claim 10 ~~66~~, wherein said treatment removes a combination of: (a) at least one receptor for alpha interferon, and (b) gamma interferon, from said fluid. --

In the Abstract:

At lines 2, please delete "different types of."

At line 3-4, please delete "other pathological factors, and antibodies to target cells" and substitute --TNFs, and receptors therefor--.

At line 5, please delete "joint or spinal fluid" and substitute --fluids from a patient, including blood, plasma, cerebrospinal fluid, synovial fluid, and the like--.

At line 6, please delete "The joint or spinal" and substitute --Following treatment, the--.

At line 7, please delete "thereafter."

REMARKS

In response to the Office Action dated **June 12, 1996**, (PTO Prosecution File Wrapper Paper No. 19), Applicants submit the following Amendment and Remarks, accompanied by request for a two-month extension of time and necessary fees. No fee for net addition of claims is required beyond those previously provided. However, if additional extensions of time or fees are necessary to prevent abandonment of this application, then payment of such extensions of time is

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hereby petitioned under 37 C.F.R. § 1.136(a), and any fees required therefor (including fees for net addition of claims) are hereby authorized to be charged to Deposit Account No. 13-2489.

In light of the most helpful comments made by the Examiner in the telephone interview on November 7, 1996, Applicants have canceled claims 1-13, 24-37, and 42-56 and added new claims 57-72. Applicants appreciate the Examiner's efforts to simplify and further the prosecution of the above-identified application toward allowance. The amendments to the specification are merely made to correct inadvertent typographical errors.

Support for each of the new claims may be found in the specification and claims as originally filed. In particular, support for claims 57 and 66, and the claims dependent thereon, may be found, for example, at page 5, lines 9-13 and at page 6, lines 21-26 of the specification. Support for the fluids used in the claimed methods may be found, for example, at page 5, lines 5-6 and at page 7, lines 13-14.

Each amendment is made to clarify the subject matter being claimed and to place the application into condition for allowance. These changes introduce no new matter, and their entry is respectfully requested.

Applicants reserve the right to further prosecute under 37 C.F.R. §§ 1.53, 1.60 or 1.62, without prejudice, subject matter which is disclosed but not claimed in the present application.

1. The Examiner's Objection to the Specification and the Rejection of Claims 1-13, 24-37 and 17-32 Under 35 U.S.C. §112, First Paragraph are Traversed.

The Examiner has maintained the objection to the specification and the rejection of claims 1-13, 24-37 and 17-32 under 35 U.S.C. §112, first paragraph, alleging that insufficient evidence has been presented to show that Applicants' claimed method of removing antigens from the fluid of a patient with autoimmune disease or AIDS is predictable. However, in view of Applicants' amendment and the clinical data submitted herewith, Applicants' respectfully traverse the Examiner's argument.

The Examiner's argument that the outcome of the presently claimed invention is unpredictable is based upon a publication by Fauci published in 1993 suggesting that an approach

to blocking cytokine secretion or action "should be explored." However, there is no reason to believe that Fauci would have known of Applicants' invention at the time of the 1993 publication, since their results had not yet been published at the time the Fauci paper was submitted. Fauci's lack of understanding is not a reason to doubt Applicants' invention.

Applicants submit two articles (attached hereto), which they have written and recently submitted to journals for publication, which clearly establish with sound clinical data, the value of the presently disclosed invention on patients with autoimmune diseases -- as disclosed in the present patent application. The articles are entitled: Paper 1 "Dramatic Long-Term Improvement in Child with Juvenile Rheumatoid Arthritis in Response to Treatment with Anti-Interferon-γ and Anti-Tumor Necrosis Factor-α Antibodies;" and Paper 2 "Anti-IFNα, Anti-IFNγ, Anti-TNFα Antibodies Singly or Combined in the Treatment of Rheumatoid Arthritis (RA) and Ankylosing Spondylitis (AS)."

Although the number of subjects within each of the four test groups is small, the results demonstrate that the combined neutralization of interferon-α ("IFNα"), interferon-γ ("IFNγ"), and/or tumor necrosis factor ("TNF") reduced inflammation in some patients within each group within one day, and *all* groups showed marked improvement by day 7. See page 2 of Paper 2. Although the treatments may be optimized for greater effectiveness in the future, the Applicants' claimed method of removing antigens from a patient with autoinnune disease or AIDS is of proven effectiveness, operating in the manner disclosed in the specification.

The present claims are drawn to a method of removing antigens from a patient with autoimmune disease or AIDS by a series of steps comprising passing fluid drawn from the patient over immunosorbent comprising a combination of antibodies (to combinations of IFNα, IFNγ,TNF, and/or the receptors therefor), followed by returning the immunosorbent-treated fluid to the patient. The test results presented in the attached papers (Paper 1 and Paper 2), although conducted to show neutralization of antigen(s) within the body of the patient, are further representative of Applicants' presently claimed method utilizing immunosorbent to remove the antigens from the blood, plasma, or the like, of the patient. Whether the clearing effect (of the combined antibodies to their corresponding antigens) occurs within the body, or extracorporeally

via an immunosorbent to which the antibody is bound, one of ordinary skill in the art could, without undue experimentation, practice Applicants' invention.

The specification need not be a blue-print for the invention. Section 112 requires only that the written disclosure of Applicants' specification be adequate to teach one of ordinary skill how to make and use, without undue experimentation, the claimed invention. *See*, *In re Parks*, 30 USPQ2d 1234, 1236 (Bd Pat. App. & Int. 1993) (literal support of the claimed invention is not required to provide adequate written description, merely conveying the concept of what is claimed in the originally-filed application is sufficient).

In the present case, the claims are directed only to the method of removing antigens from a patient with autoimmune disease or AIDS by a series of steps including passing fluid drawn from the patient over immunosorbent comprising an expressly defined combination of antibodies. However, in the present case, Applicants' specification not only teaches how to practice the claimed methods of removing antigens, the effectiveness of the methods is further supported by newly released clinical data.

The clinical results do not have to be obtained in exactly the same way as the method claimed in the invention to demonstrate the predictability of the disclosure, because the data is not intended to elucidate or supplement Applicants' specification as it relates to the claimed method. Rather, the data demonstrates the efficacy of the principles behind Applicants' claimed method, showing that the effect of the combined antibodies on the antigens, specifically on the autoimmune disease-related antigens occurs as disclosed in the specification. In other words, the data confirms the predicted outcome of the method as disclosed in the application, and illustrating Applicants' compliance with 37 C.F.R. §112.

Those familiar with antigen/antibody reactions would readily understand the effectiveness of Applicants' claimed method in light of the successful neutralization of antigens by the corresponding antibodies as disclosed in Applicants' Papers 1 and 2, which utilize essentially the same antibody combinations as are disclosed in Applicants' specification. A detailed description of the basic principles behind an antigen/antibody reaction was not provided by Applicants.

However, the specification need not disclose, and preferably omits that which is well known in the art. *See, Ex parte Obukowitz*, 27 USPQ2d 1063, 1067 (Bd. Pat. App. & Int. 1992).

To emphasize that fact that Applicants did, indeed, predict the outcome now proven by objective evidence, the Examiner is referred to the excellent description by Dr. Skurkovich of his invention in the January 23, 1996 Response to the Office Action dated August 23, 1996, and a comparison of his work with that of others attempting to treat the manifestations of autoimmune disease in patients. The numerous publications cited with the January 23, 1996 Response clearly demonstrate the state of the art, illustrating the standard of understanding by those studying the problems involved in treating autoimmune disease in a patient, and showing their comprehension of the antigen/antibody reaction. However, the publications also emphasize the frustrations of the scientists attempting to find a solution, and suggest their goals for the future. Thus, although the publications establish the state-of-the-art at the filing date of the application, they fail to anticipate or obviate Applicants' invention.

These publications were not cited under Rule 56, since other than Drs. Skurkovich and Skurkovich's own work, prior publications are not material to the claimed invention. They merely establish the state of the art under which the invention was first disclosed, and the present standards under which scientists in the field operate. The work by the Drs. Skurkovich and Skurkovich was, and continues to be, pioneering in the treatment of patients with autoimmune diseases. See, page 194, col. 1, Vilĉek *et al.*, "The Role of Interferon in AIDS," In AIDS: The Epidemic of Kaposi's Sarcoma and Opportunistic Infections, AE Friedman-Kien & LJ Laubenstein, eds. Masson Publishing. New York 1986 (copy attached to show state-of-the-art). Yet the predictability of Applicants' claimed method utilizing antibodies to IFNα, to IFNγ and/or to TNF, or their receptors to remove IFNα, IFNγ and/or TNF is represented by the outstanding results obtained at clinical trial.

The Examiner has also questioned at page 2 of the outstanding Office Action, whether Applicants have a "sufficient basis to predict whether removal of these mediators by plasmapheresis using antibody affinity devices will mediate effective therapy of AIDS and all autoimmune diseases." The Examiner's comments, however, are irrelevant to the presently

claimed invention. Applicants do not, in the present application, *per se* claim a method of effectively treating either AIDS or autoimmune disease. Rather, Applicants' claims are directed only to the removal of antigens from a patient with autoimmune disease or AIDS in accordance with a series of defined steps involving passing fluid drawn from the patient over an immunosorbent comprising a combination of antibodies.

Nevertheless, the importance of Applicants' claimed method is soundly supported as a potential treatment of autoimmune disease and AIDS based upon the Applicants' submitted data (Papers 1 & 2), taken together with the state of the art as established by the publications submitted with Applicants Response dated January 23, 1996 in combination with recently published research by Gringeri *et al.*, "Absence of Clinical, Virological, and Immunological Signs of Progression in HIV-1-Infected Patients Receiving Active Anti-Interferon-α Immunization: A 30-Month Follow-Up Report," *J. Acquired Immune Deficiency Syndromes and Human Retroviralogy 13*:55-67 (1996). A copy of the Gringeri *et al.* paper is attached to further establish the state of the art. Gringeri *et al.*, citing the work of Skurkovich *et al.*, confirm that anti-IFN-α immunized HIV- positive patients showed a significant and reproducible decrease in circulating IFN-α titers as compared with untreated patient, which also proved to be a singular predictor of a favorable prognosis.

Consequently, sound objective evidence indicates the value of removing or neutralizing interferons (α and/or γ) and/or TNF, or their receptors, in AIDS patients as well as in patients with autoimmune disease, as exemplified at least by rheumatoid arthritis and ankylosing spondylitis. This merely gives greater credibility to Applicants' claims which are directed to removing antigens from a patient with autoimmune disease or AIDS. Applicants need not prove that the practice of Applicants' claimed method constitutes an effective treatment for autoimmune disease or AIDS.

Consequently, Applicants respectfully seek reexamination of the claims as amended, which are believed to be in full compliance with all of the requirements of 35 U.S.C. § 112.

2. The Examiner's Rejections of Claims 1-13, 24-37 and 17-32 Under 35 U.S.C. §102 and §103 are Traversed.

The Examiner has maintained a series of rejections of claims 1-13, 24-37 and 17-32 under 35 U.S.C. §102 and §103 over the combined patents of Skurkovich and Skurkovich *et al.* (U.S. 4,362,155; 4,605,394 and 4,824,432) in further view of the Moeller patent (U.S. 5,123,024). On the whole, however, the Examiner's rejections are moot in light of Applicants' amendment.

The presently claimed method of removing antigens from a patient with autoimmune disease or AIDS is neither anticipated not suggested as obvious in view of the cited prior art. Applicants' cited earlier patents each claim a method of treating a patient or treating a disease.

U.S. 4,362,155 claims a "method of treatment" comprising extracorporeally absorbing "interferon" from the fluid of a patient. The term "interferon" was generically used in the `155 specification, without definition of IFNα or IFNγ at the filing date in 1981. However, related work at the time was directed to what is now generally considered alpha interferon. See, e.g., U.S. 4,172,071 and 4,168,261. In any case, the disclosure of the `155 patent makes no reference what-so-ever to any combination of anti-IFNα and anti-IFNγ or to either one in combination with an anti-TNF. As a matter of fact, there is no mention of IFNα, IFNγ or TNF or their antibodies or receptors in the `155 disclosure. Moreover, there is no suggested combination of any antibodies in an immunosorbent for the removal of antigens from a patient in the `155 patent.

There is a `155 disclosure of, and a claim to, the use of a combined sorbent "to remove both interferon and autoantibodies from the blood of a patient" (col. 3). However, the present invention does not claim any immunosorbance of a "autoantibody." The `155 patent also discloses and claims, the combined use of a first sorbent for interferon with a second sorbent. The second sorbent is not defined, but at most it could be selected only from the antibodies discussed in the `155 specification - antibodies against cardiac tissue or anti-IgE. Since antibodies to IFNα, IFNγ or TNF are not mentioned in the `155 patent, a method comprising a step which utilizes an immunosorbent comprising a combination of anti-IFNα, anti-IFNγ and/or anti-TNF and/or antibodies to their receptors is neither anticipated nor obviated by the patent.

U.S. 4,605,394 claims an *improved* "method of treating diseases" comprising extracorporeally absorbing "interferon" from the fluid of a patient as in the `155 patent, and further comprising a step of administering normal interferon to the patient after completing the process of clearing the defective interferon from his blood or plasma. There is no suggested combination of any antibodies in an immunosorbent for the removal of antigens from a patient in the `394 patent. But, there is a disclosure of, and a claim to, the use of a "combined sorbent . . . for absorbing interferon from the plasma or plasma with leukocytes and a second component that selectively absorbs blocking antibodies . . . " (col. 4, lines 64-67). However, the present invention does not claim any immunosorbence of an "antibody" or a "blocking antibody." Consequently, since antibodies to IFNα, IFNγ or TNF are not mentioned in the `394 patent, removal of antigens (IFNα, IFNγ or TNF and/or their receptors) from a patient by a method comprising a step of passing fluid over an immunosorbent comprising a combination of anti-IFNα, anti-IFNγ and/or anti-TNF and/or antibodies to their receptors is neither anticipated nor obviated by the `394 patent.

U.S. 4,824,432 claims a "method of treatment of mammals having immunodisorders" or a "method of treatment of humans having an acquired immune deficiency syndrome (AIDS) associated with the disturbance of the synthesis of interferons and the production of defective interferons" having an *improvement* comprising the parenteral administration to the body of several substances. The administered substances are defined in the claims as "interferon clearing agent," "RNA nuclease," and "antibody to HTLV-III/LAV." The interferon cleared by the "interferon clearing agent" is specifically defined in claims 6 and 7 as "alpha interferon" and the interferon clearing agent is "antibody to alpha interferon." In claim 33, gamma interferon is cleared by the "interferon clearing agent," the interferon clearing agent is "antibody to gamma interferon."

To show that Applicants have previously disclosed the use of combined interferons, the Examiner points to col. 2, lines 30-34 of the `432 patent, disclosing the treatment of AIDS and other autoimmune disorders by the IM of IV introduction into the patient of "antibodies to alpha IFN, specifically antibodies to pH labile alpha IFN and antibodies to other types of IFNs or

defective IFNs." But the Examiner's interpretation is misdirected. It is well known in the art that there are numerous subtypes of alpha interferon (*e.g.*, IFN-α1, IFN-α2, etc.). Hence, Applicants' reference to "other types of IFNs or defective IFNs," was directed to subtypes of *alpha* interferon, other than pH labile alpha IFN. Evidence that Applicants never intended the term "other IFNs" as used in this sentence to refer to IFNγ can be found at lines 39-42 in the same column. There, Applicants discuss the further treatment of AIDS patients with "normal gamma IFN." Logic would preclude describing the removal of IFNγ in one sentence and its subsequent administration immediately afterwards. Thus, the Examiner's reading of the `432 patent to obviate Applicants' presently claimed invention is unsubstantiated.

As in the `394 patent, there is a disclosure in the `432 patent of the use of a "combined sorbent . . . for absorbing interferon from the plasma or plasma with leukocytes and a second component that selectively absorbs blocking antibodies . . . " (col. 6, lines 25-29). However, the present invention does not claim any immunosorbance of an "antibody" or a "blocking antibody." Moreover, there is no suggested combination of any antibodies in an immunosorbent for the removal of antigens from a patient in the `432 patent. Consequently, since neither combining the antibodies to IFNα and IFNγ, nor TNF (antigen or antibody) are mentioned in the `432 patent removal of antigens (IFNα, IFNγ or TNF and/or their receptors) from a patient by a method comprising a step of passing fluid over an immunosorbent comprising a *combination* of anti-IFNα, anti-IFNγ and/or anti-TNF and/or antibodies to their receptors is neither anticipated nor obviated by the `432 patent.

Adding the Moeller patent (U.S. 5,231,024) cannot correct the deficiencies in the argument that Applicants' own patents anticipate or obviate the presently claimed method of removing antigens from a patient with autoimmune disease or AIDS comprising passing fluid drawn from the patient over an immunosorbent comprising a combination of anti-IFNα, anti-IFNγ and/or anti-TNF and/or antibodies to their receptors. Moeller claims, and indeed teaches, only hybridoma cell lines which synthesize highly specific monoclonal antibodies against TNF, the thus-produced monoclonal antibody against TNF, processes for preparing the TNF hybridoma cell lines and antibodies, and use of the TNF monoclonal antibodies. However, Moeller adds nothing

to Applicants' earlier patents that would suggest Applicants' presently claimed invention. To begin with, the Moeller hybridoma cell line and monoclonal antibody are very specific, encompassing only the deposited species. However, Moeller also fails to suggest any basis for combining the TNF monoclonal antibody with any other type of antibody to remove a plurality of antigens from the fluid passed over an immunosorbent comprising a plurality of antibodies.

It is impermissible to choose parts of several patents and publications, selectively ignoring other information disclosed therein, and in hindsight to piece together Applicants' invention using Applicants' own disclosure as the pattern, absent a showing in the art that suggests the combination. It is the "suggestion in the art," that the antibodies be combined in the manner disclosed by Applicants in the presently claimed invention, which is missing from the Examiner's argument based upon the dicta in *In re Kerkhoven*, 205 USPQ 1069 (CCPA 1980) that prior art approaches may be logically combined. The test for establishing obviousness by combining teachings in the prior art, according to the CAFC in *In re GPAC.*, 35 USPQ2d 1116, 1123 (Fed. Cir. 1995) is "what the combined teachings would have suggested to those of ordinary skill in the art." Yet no one, not even the present Applicants, prior to the present invention had considered *combining* the antibodies to remove antigens in the manner now claimed. No data was available to lead one to believe that, even though the use of individual antibodies and of the combined used of antibodies with certain antigens had been suggested in the art, there was any basis for combining the expressly disclosed antibodies in the manner now claimed to removed antigens from a patient with autoimmune disease or AIDS.

It is irrelevant that there is a showing in the prior art that Applicants previously disclosed the use of an immunosorbent containing anti-IFNα to treat a patient with autoimmune disease, or that Applicants' previously disclosed the use of an immunosorbent anti-IFNα in combination with a sorbent to absorb antibodies (blocking antibodies, autoantibodies, etc.) from the fluid being passed over the sorbent. The very fact that Applicants have previously disclosed combined substances in the immunosorbent, but that they did not suggest an immunosorbent comprising both anti-IFNα and anti-IFNγ, is a clear indication that the Applicants' would have unambiguously defined the combination earlier, had that been their intent. They did not. Thus,

the basis for combining their previous disclosures in the manner proposed by the Examiner is without merit. *See, Ex parte Marinaccio*, 10 USPQ2d 1716, 1717 (Bd. Pat. App. & Int. 1989) (the question under 35 USC §103 is not what the routineer *could have done*, but what would have been obvious for such a person to do).

Similarly, Moeller discloses certain hybridoma cells and monoclonal antibodies specific for TNF, but offers no suggestion that they be combined in an immunosorbent with one or more antibodies to interferon or to an interferon receptor to remove antigens from fluid being passed over the combination. Nor do Applicants previous disclosures suggest such a combination, since TNF is not even mentioned. Nor does any reference or combination of references in the prior art suggest such a combination.

Accordingly, Applicants respectfully submit that there is no basis for rejection under 35 U.S.C. §102, since in every prior art reference at least one element is missing from the teaching that would anticipate Applicants' presently claimed method for removing antigens from a patient with autoimmune disease or AIDS comprising passing fluid drawn from the patient over an immunosorbent comprising a combination of anti-IFNα, anti-IFNγ and/or anti-TNF and/or antibodies to their receptors. Also, Applicants respectfully submit that there is no basis for rejection under 35 U.S.C. §103, since there is no reference, or combination of references, that suggest combining selected components of the prior art in the manner suggested. Therefore, Applicants ask that the claims be reconsidered in light of the above arguments, and that all rejections made under 35 U.S.C. §102 or 35 U.S.C. §103 be withdrawn.

3. Conclusion

Applicants believe that all stated grounds of objection and rejection have been properly traversed, accommodated, or rendered moot. Applicants therefore respectfully request that the Examiner reconsider all presently outstanding objections and rejections, and that they be withdrawn. It is believed that a full and complete response has been made to the outstanding

Office Action and, as such, the present application is in condition for allowance. If the Examiner believes, for any reason, that personal communication will expedite prosecution of this application, the Examiner is invited to telephone Applicants' undersigned representative at (703) 716-5240.

Prompt and favorable consideration of this Amendment is respectfully requested.

Respectfully submitted,

Evelyn H. McConathy

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Attorney for Applicants
Registration No. 35,279

Date: November 8, 1996

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